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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,856	SOLOMON ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *9 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *15 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment filed 6-29-06 has been entered into the record and has been fully considered.

2. The terminal disclaimer of 6,919,075 submitted 6-29-06 has been accepted.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the examiner.

5. Claims 1-12 are pending and under examination as submitted 3-8-05. Claims 13-17 have been canceled.

Election/Restrictions

6. Applicant's election of Group I, claims 1-12, in the reply, filed 3-8-05 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of species of SEQ ID NO:1 (EFRH) in the reply filed on 10-19-05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants state that all claims read on the elected species as SEQ ID NO:1 is shared amongst all sequence members. However, a search for SEQ ID NO:1 is not co-extensive to all other members. Further SEQ ID NO:1 is anticipated by the prior art as noted below. Accordingly, claim 8 is

presently non-linking with respect to SEQ ID NO:1 and the other sequences denoted in claim 9.

Claim 9 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Applicant's response of 6-29-06, particularly the traversal of the species election requirement, and withdrawal of claims 9 and 11, is noted as set forth at pp. 2-4 of the response. Applicant's note the confusion of the office action in that claim 9 and 11 are subject to obviousness rejections as set forth in the non-final action of 12-29-05.

In response, this inadvertent error is acknowledged. As claims 9 and 11 are drawn to patentably distinct sequences and the sequences are not co-extensive in search and examination with respect to elected SEQ ID NO:1, these claims are withdrawn. Grounds of rejection over these claims is also withdrawn to correct the confusion on this matter. It is however, noted for the record that the EFRH peptide is within the sequences of claims 9 and 11. Upon indication of allowable subject matter, rejoinder may be possible. However, as the claims are not instantly indicated to be allowable, rejoinder is not persuasive and the claims remain withdrawn.

Priority

7. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the limitations of claims 5, and 7. Accordingly the effective filing date for the limitations recited in these claims is the filing

date of 7-15-03. Traversal should indicate where specific support for the noted limitations may be found within the provisional application.

Applicant's traversal at pp. 4-5 and guidance to 09/473,653, filed 12-29-1999 now US 6,703,015 is noted. The document is a continuation. The Examiner also notes the provisional, 60/152,417 filed 9-3-1999. No intervening references are cited.

Double Patenting Rejections

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-8, 10, and 12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20, especially claims 11-13 and 17-20 of copending Application No. 11/073,526. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '526 claims stipulate a species of the instant invention thereby fairly anticipating instant generic claims. In particular, the instant application claims a method of inhibiting aggregation of β-amyloid in a subject or disaggregating aggregated β-amyloid in a subject comprising administering to a subject in need thereof an effective

amount of a filamentous bacteriophage which displays an epitope of β-amyloid so as to elicit antibodies against said epitope in said subject, wherein said antibodies inhibit aggregation of said β-amyloid in said subject and/or cause disaggregation of said β-amyloid aggregate in said subject. The application 11/073,526 claims a method of treating Alzheimer's disease by introducing a pharmacological composition in a subject in need thereof to inhibiting aggregation of β-amyloid in a subject and treat the disease. The subject pharmaceutical compositions are directed to the same, a phage virus particle displaying a polypeptide that comprises at least one epitope of beta amyloid (claim 1 of '526). In the '526 Appliation, claim 13 recites the virus is a bacteriophage, and claim 17 recites to inhibit aggregation of beta-amyloid as in claim 1 of the instant application. The instant application does not teach administering the bacteriophage as a composition to treat Alzheimer's disease. However, the treatment of Alzheimer's disease is a species member of diseases recognized as requiring inhibition of aggregation of β-amyloid peptide. Since both applications teach inhibiting aggregation or removal of amyloid, the patenting of the co-pending claims would render obvious the instant Application directed to the generic mechanism of action or function of the Alzheimer's treatment. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants request in the response of 6-29-06 that the double patenting rejection be held in abeyance until such time that a notice of allowance is issued. No comments as to the correctness of the rejection have been noted.

Rejection is maintained as set forth in MPEP 804, the "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 8 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Schenk et al. WO 99/27944, 10 June 1999 (IDS AE, 7-15-03).

12. Claims 1, 8 and 12 are also rejected under 35 U.S.C. 102(e) as being anticipated by, Schenk 6,787,139, Sept 7, 2004.

The aforementioned WO 99/27944 and 6,787,139 references are cumulative. The patent extends to priority dates of 60/067,740 (12-02-97) and 60/067,740 (04-07-

98). The citations noted below are in reference to the WO 99/27944 publication. However the teachings are identical and the reasoning is therefore noted to be the same for both references.

Schenk et al. teach administration of β-amyloid immunogens (pg 3) to a patient in order to generate antibodies to prevent formation of amyloid plaques or dissolve existing plaques. The epitopes administered are inclusive of multiple species within or full length β-amyloid of recognized species 1-40, 1-42 and 1-43 and accordingly comprise the noted epitopes of SEQ ID NO:1, Such plaques are of aggregated Beta-amyloid in a subject, particularly of Alzheimer's disease patient. The plaques are areas of disorganized neuropil with extracellular amyloid deposits at the center visible by microscopic analysis of sections of brain tissue (Background). The reference teaches administration including intranasally, as in claim 12 (pg 4, line 17), of an agent, which includes immunogens, antibodies, active fragments, or derivatives of the antibody (pg 3, line 6-8), effective to induce an immunogenic response against aggregated Aβ in a patient as in claim 1 (pg 2, line 34-36; pg 3, lines 18-20). The reference teaches A β 39, 40, 41, 42, or 43 (pg 3, line 28 and Summary); thus, comprising the relevant sequences as claimed in claim 8 and9 (SEQ ID NO:3, Aβ 1-43). The reference teaches analysis of an effective amount via measurement of antibody titers and notes amounts inclusive of 1.0 µg or 10 µg or 50 µg or 100 µg (pg 3, line 25-7) effective to elicit antibodies and to effect removal or inhibiton of plaque production/deposition. Schenk teaches mice, which developed a high antibody titer, including titers greater than 1/10,000 (see Figure 1). The highest antibody titers were generated with Freund's adjuvant with a peak GMT

of about 87,000 as determined by ELISA. Schenk disclose if monitoring indicates a reduction of the immune response over time, the patient can be given one or more further doses of the agent (pg 4). Schenk discloses administration under conditions to generate a beneficial immune response (pg 2, line 35). Schenk et al. also teach the agent administered may be displayed via nucleic acid production for presentation within the host and expressed upon the surface of a virus or bacteria, specifically via phage (bacteriophage) display methods (pg 3, line 28; pg 16, and 17, line 10-11) with reference noted therein to the art recognized teachings of Devlin, WO91/18980 as in claim 1 and that peptide libraries can be generated by phage display methods (pg 16-17). Thus, the reference teachings anticipate claims 1, 8 and 12.

Applicant's traverse this rejection at pp. 7-9 of the 6-29-06 response. These arguments have been fully considered but are not persuasive. In particular, applicant's take the position that the cumulative Schenk references (cited independently) do not fairly teach administration of bacteriophage itself, as a delivery vehicle, and for displaying the antigen in question. Applicants acknowledge the teachings of Schenk throughout pp. 16-17 but argue that the description of screening for useful peptides via phage technology does not arrive at administration of phage directly. However, the therapeutic agents are further noted throughout pp. 14-16, particularly to include agents that induce the requisite immune response, either actively or passively. As at p. 16, the therapeutic agent is inclusive of a virus or bacteria. Bacteriophage or "phage" is a virus, see Devlin WO91/18980. For further clarity and understanding, Applicant's are further referred to the common Wikipedia definition of bacteriphage, M13 phage or M13 virus.

Schenk is on point to administration using, "a viral or bacterial vaccine," see in particular p. 16, lines 11-33. As is commonly recognized in the art, this technology allows for expression of the desired peptide epitope within the larger context of a virus or bacteria. As described in Schenk, "A nucleic acid is incorporated into a genome or episome of the virus or bacteria. Optionally, the nucleic acid is incorporated in such a manner that the immunogenic peptide is expressed as a secreted protein or as a fusion protein with an outersurface protein of a virus or a transmembrane protein of a bacteria so that the peptide is displayed. Viruses or bacteria used in such methods should be nonpathogenic or attenuated." This is exactly the technology of phage display, the peptide epitiope desired is expressed by the virus. Accordingly Schenk teaches administration of such a virus as a vaccine not only via direct administration, but further via arrival at such administration using phage peptide display for evaluating compounds in vivo as at p. 17.

Accordingly, Schenk does clearly intend for the administration of either viruses or bacteria directly that are modified to express beta amyloid peptides and/or epitopes. Schenk further directs to sequences of beta amyloid which comprise EFRH of SEQ ID NO:1. While bacteriophage virus is not listed at p. 16, lines 20-21, it is particularly noted to be useful as denoted at p. 17, lines 10-11. It is true, as applicant's point out, that bacteriophage is particularly noted in the paragraph at p. 17 with respect to screening of peptide libraries. However, this exemplification by Schenk for use of bacteriophage in screening constructs and to determine the peptides that are preferred for delivery (for example via requisite stimulation of Abeta immunity, or reaction with beta-amyloid

antibodies) does not detract. Instead, it evidences the suitability and selection of bacteriophage as intended, as a virus capable of providing the noted functional activities of a therapeutic agent via peptide display as described at pp. 16, lines 16-20. The Schenk reference guides to bacteriphage as a viral construct that achieves peptide display expression for example of beta-amyloid peptides as preferred. Accordingly, the virus is at once a preferred vaccination vector and therapeutic compound or agent.

Moreover the screening of these compounds is noted to be possible in vivo in transgenic animals for example. Accordingly, even the screening protocol itself arrives at the in vivo administration of bacteriphage constructs that display beta amyloid peptides on their surface, are reactive with beta amyloid antibodies or stimulate such an immune response. Accordingly, the screening method exemplifies the suitability of bacteriphage as a virus for selection and expression of peptide epitopes displayed on its surface as noted by Schenk for vaccine purposes. As in claim 1, all that is required is for this construct's administration in a subject. Schenk teaches the requisite evaluation via antibody binding and stimulation of and immune response.

In addition, there is no doubt that the peptides and/or epitopes of Schenk are of beta-amyloid or specific to beta-amyloid that comprises the sequence of SEQ ID NO:1, EFRH. Accordingly, the Schenk constructs are on point to the presentation of SEQ ID NO:1, see for example p. 16, lines 11-12 and throughout p. 17, via bacteriphage, see also claim 28-29, 44, and 50-51. Additionally, the intranasal route is noted for the therapeutic agents of Schenk, including the viral or bacterial constructs, see p. 29. Thus, the references fairly anticipate the claimed invention.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-8, 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Schenk et al. WO 99/27944, 10 June 1999, or Schenk 6,787,139 Sept 7, 2004 (cumulative to WO 99/27944 priority extending to 60/067,740 (12-02-97) and 60/067,740 (04-07-98)), each alternatively in view of Devlin, WO91/18980, 12 December 1991, Willis A, Gene 128(1):79-83, 1993 (IDS 7-15-03, CC), and Bhardwaj et al., Journal of Immunological Methods, 1995, 179:165-175.

Schenk et al., each teach as set forth above meeting the limitations of claim 1, 8 and 12. However, neither Schenk reference explicitly teaches selection of bacteriphage

species fd or M13 as in claims 4 and 7, having the properties of the limitations of claims 2-3.

Devlin et al., teach selection of filamentous bacteriophage fd and M13 for preferred production and presentation of peptide antigen, see in particular p. 6, lines 19-26.

The limitations of claims 2-3 are intrinsic properties of bacteriophage fd and M13 as evidenced by Bhardwaj. The filamentous phages are single stranded DNA phages which infect male specific E. coli strains (a normal constituent of host bacterial microflora), see in particular Bhardwaj et al., Journal of Immunological Methods, 1995, 179:165-175, p. 165, column 2.

Schenk et al. also do not teach the limitation of claims 6, 10 and 11 where the eptiopes of Beta-amyloid are displayed via coat glycoprotein VIII on said bacteriophage.

Bhardwaj et al., (Journal of Immunological Methods, 1995, 179:165-175) teach selection of fd or M13 fusion constructs. Bhardwaj notes the advantages of VIIIp (glycoprotein) fusions for production and expression of foreign peptide epitope constructsin analyzing binding interactions interactions and the further benefit of the availability of specific monoclonal antibodies to either the minor (gIIIp) and major (gVIIIp) coat proteins of phage for analysis of expression, see in particular abstract and experimentation throughout.

Willis et al further teach that the genome of bacteriophage fd has been engineered to permit construction of hybrid virus particles in which the wild-type major coat protein (gpVIII) subunits were interspersed with coat proteins displaying one or

other of two foreign peptides (fdMAL1, sequence NANPNANPNANP or fdMAL2, sequence NDDSYIPSAEKI) in the exposed N-terminal segments [Greenwood et al., J. Mol. Biol. 220 (1991) 821-827]. These sequences represent major antigenic determinants of the circumsporozoite protein of the malaria parasite, Plasmodium falciparum. The peptide epitopes in the hybrid bacteriophages were found to be strongly immunogenic in four different strains of mice without the use of external adjuvants, and the antibodies (Ab) were highly specific to the individual epitopes in ELISA assays. When tested in nude (nu/nu) and heterozygote (nu +/-) BALB/c mice, the immune response was found to be T-cell dependent and to undergo class-switching from IgM to IgG. Proliferation assays of T-cells taken from lymph nodes of BALB/c mice injected with bacteriophage particles in the presence or absence of Freund's complete adjuvant indicated no difference in the immune response. This way of generating Ab against peptide epitopes is simpler and much less expensive than the conventional method of peptide synthesis and coupling to a carrier protein for injection. The specificity of the immune response, the ability to recruit helper T-cells and the lack of need for external adjuvants suggest that it will also be an inexpensive and simple route to the production of effective vaccines, see in particular abstract.

The artisan would have been motivated to select gpVIII constructs of either phage fd or phage M13 for expression of the Schenk epitiopes of Abeta noted to comprise the elements of SEQ ID NO:1, evidenced to stimulate the appropriate immune response for inhibiting aggregation or providing for disaggregation of amyloid plaques. One of skill would be motivated to use phage expression as motivated by Schenk and

further motivated by Bhardwaj and Willis to select gpVIII constructs for the recognized advantages of such vector constructs in providing expression, ease in analysis and stimulation of an immune response in the host. One of skill in the art would have expected success using such presentation of antigen given the art recognized evidence for the suitability of the relevant epitiopes for expression (Schenk), the high skill in the art of such expression using bacteriophage constructs (Bhardwaj, Willis and Devlin) and the advantages of gpVIII constructs in producing an immunogenic response and for ease of analysis of expression (Bhardwaj and Willis).

With respect to claim 5, the Examiner notes that the claim limitation is directed to steps to achieve administration such that a titer of antibodies is produced above 1:50,000. Schenk notes analysis of peptide expression such that titers are produced (so as to be effective in treatment and inhibition of aggregation of bet amyloid) such that the titers are directed to about 1:87,000 as determined by ELISA. The dosage is noted to be suitably tested and determined whether via peptide administration or via phage vector. In particular, Schenk teaches analysis of an effective amount via measurement of antibody titers and notes amounts inclusive of 1.0 µg or 10 µg or 50 µg or 100 µg (pg 3, line 25-7) effective to elicit antibodies and to effect removal or inhibiton of plaque production/deposition. Schenk teaches mice, which developed a high antibody titer, including titers greater than 1/10,000 (see Figure 1). The highest antibody titers were generated with Freund's adjuvant with a peak GMT of about 87,000 as determined by ELISA. Schenk disclose if monitoring indicates a reduction of the immune response over time, the patient can be given one or more further doses of the agent (pg 4).

Schenk discloses administration under conditions to generate a beneficial immune response (pg 2, line 35). Schenk et al. also teach the agent administered may be displayed via nucleic acid production for presentation within the host and expressed upon the surface of a virus or bacteria, specifically via phage (bacteriophage) display methods (pg 3, line 28; pg 16, and 17, line 10-11) with reference noted therein to the art recognized teachings of Devlin, WO91/18980 as in claim 1 and that peptide libraries can be generated by phage display methods (pg 16-7). Accordingly, the artisan is motivated to provide phage dosage to mice such that at time point 30 days or less the titer is at least 1:50,00 as determined by ELISA. This corresponds to one of the most effective Schenk treatment regimes with AN1792 and 1528. In particular, "Mice were bled four to seven days following each immunization starting after the second immunization, for a total of five bleeds. Antibody titers were measured as A.beta.1-42-binding antibody using a sandwich ELISA with plastic multi-well plates coated with A.beta.1-42. As shown in FIG. 13, peak antibody titers were elicited following the fourth dose for those four vaccines which elicited the highest titers of AN1792-specific antibodies: AN1792 (peak GMT: 94,647), AN1528 (peak GMT: 88,231), A.beta.1-12 conjugate (peak GMT: 47,216)and rodent A.beta.1-42 (peak GMT: 10,766)." Accordingly, the reference teachings render the invention obvious to the artisan.

Applicant's traverse the rejection as set forth in the 6-29-06 response, pp. 9-12. Specifically Applicant's assert that Schenk does not arrive at a filamentous bacteriophage which displays an epitope of beta amyloid as claimed. Yet as discussed above Schenk provides guidance to peptide libraries generated by phage display

methods, see in particular p. 17, lines 9-11, guide to beta amyloid peptides, fragments, epitopes and analogs with beta-amyloid antibody immunoreactivity, see p. 13-15 and such peptides that may be presented as viral or bacterial vaccines, particularly where the nucleic acid is incorporated into a genome or episome of a virus or bacteria, see p. 16, lines 11-22. Accordingly, these limitations are fairly met.

Applicant's argue that Devlin does not suggest bacteriphage bearing foreign proteins for vaccine purposes. While Devlin does not use this wording Devlin does teach the use of phage constructs to express peptide products and to evaluate the peptide molecules for their biological activity, as well as their therapeutic and prophylactic applications, see in particular abstract and pp. 2-12. These evaluations may take place within the context of the recombinant virus and with expression in suitable host cells. Accordingly, the peptide constructs are presented to host cells in the form of viral particles and therefore approximate a viral vaccine.

Nevertheless, Schenk was relied on for the noted teaching with respect to administration of virus as vaccine. Devlin was utilitzed to further evidence that bacteriophage fd and M13 are such suitable bacteriophage viral vectors, ie., constructs capable of expressing the beta amyloid peptides to the host cells. Bhardwaj does teach as summarized by Applicant's but is not needed to supplement the teaching of bacteriphage as a suitable viral vaccine vector. Willis is not disparaged as Willis was relied on for the teaching of gpVIII bacteriophage constructs. Brain delivery is not a noted claim limitation. Titer formation is not evidenced to be an unexpected property where the regime of Schenk is noted to provide guidance to the required titer. Schenk

provides guidance to the common skill of the artisan in achieving a suitable antibody response in vivo and assays to monitor the response to any particular antigen formulation.

The vaccine may be further considered a DNA vaccine as described in the sense that it is of recombinantly produced phage particles that are packaged and presented to the host and which stimulate the immune response.

Similarly, intranasal vaccination is stipulated by Schenk. Schenk's guidance is further on point to beta amyloid peptide constructs and the stimulation of requisite immunoreactivity. Accordinlgy, evidence of nonobviousness is not found where no comparison arrives at any property or element that is not expected via the combination of the prior art that arrives at administration of the suitably modified phage constructs to present beta-amyloid peptide constructs to the host. Solomon is cited solely to evidence disaggregation of site directed mab directed to beta-amyloid 1-28 epitope. Accordingly, it is cumulative to Schenk and not critical.

16. Claims 1-8, 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schenk et al. WO 99/27944, 10 June 1999, or Schenk 6,787,139 Sept 7, 2004 (cumulative to WO 99/27944 priority extending to 60/067,740 (12-02-97) and 60/067,740 (04-07-98)), Frenkel et al., Journal of Neuroimmunology, 1 August 1998, 88:85-90 (IDS reference AU; 7-15-03), Fanutti et al., SIB Biochem. Soc. Trans., Phage-display of antigenic peptides applied to vaccine design, 120, 1998 and Delmastro et al., Vaccine 15(11):1276-85, 1997, in view of Bhardwaj et al., Journal of

Immunological Methods, 1995, 179:165-175 and as evidenced by Winter et al., Ann Rev Immunol, 1994, 12:433-455.

Schenk et al., teach as set forth above inlcudng the limitations of claims 1, 8 and 12, but do not teach specific construct of phage fd (or M13) expressing EFRH peptide.

Frenkel et al. (1998) teach anti-aggregating antibodies that bind to an epitope located as a continuous sequence at the beginning of the N-terminal of ß-AP, and contemplates use of the peptide to control aggregation of ß-AP in vivo (pg 86 and Results). The reference teaches (pg 85 and 86) epitope libraries in which different peptides are expressed on the surface of filamentous phage, including the peptide EFRH (Table 1) as in claim 8, which inhibits binding of monoclonal antibodies to ß-amyloid peptide (claim 1). The reference teaches infecting E. coli K91 cells; and thus, the reference meets the limitations of a bacteriophage that propogates in bacterial flora in said recipient and in E. coli (claims 2-3). Frenkel's bacteriophagephage is an Fd-derived vector thereby meeting claim 4.

Frenkel et al. do not teach use of the antigen displayed on the surface of a bacteriophage M13 (claim 7) nor does it teach the epitope is displayed via coat glycoprotein VIII (claim 6 and 10).

Fanutti et al., teach phage-display of antigenic peptides applied to vaccine design using bacteriphage fd and gVIIIp for expression of HIV epitiopes to be used in vivo stimulate immunity via immunization with phage particles.

Delmastro et al., further teach the in vivo administration of filamentous phage M13 for display of HCV peptides via either intragastric or intranasal vaccination in mice.

The vaccination procedures are noted to be effective in the stimulation of an immune response, specifically high titers of specific antibodies both systemically and in mucosal secretions noting the particular advantages of intranasal induction, see Discussion pp. 1283-84.

Bhardwaj et al., (Journal of Immunological Methods, 1995, 179:165-175) teach fd or M13 bacteriphage for production of antibodies which react with the minor (gIIIp) and major (gVIIIp) coat proteins of phage M13. Bhardwaj also teaches constructs using these peptides for expression of foreign proteins in phage display and the advantages of such constructs in evaluating expression via monoclonal antibodies to the fused protein. Further, Winters et al. (1994) discloses selecting human antibodies of desired specificity.

It would have been obvious to one of ordinary skill in the art to use the teachings of Schenk, Frenkel et al., Fanutti et al., and Delmastro et al., to use the bacteriophages fd or M13 to express the ß-amyloid epitopes for the purpose of presenting the antigen to the immune system within the host for production of antibodies, including via intranasal vaccination routes. The person of ordinary skill in the art further would have been motivated to use the filamentous bacteriophage taught by Schenk, Bhardwaj et al., Fanutti et al., Delmastro et al., and Frenkel et al., that expresses foreign peptides or proteins displayed via coat glycoprotein VIII because Bhardwaj et al. teaches the advantages of their vector system in detection of foreign proteins through the use of the isolated monoclonal antibodies directed to glycoprotein VIII, and would have expected success because both Fanutti, Delmastro, Bhardwaj et al. and Frenkel et al., teach the

use of the phage vectors for expressing foreign peptide and to stimulate the appropriate immune response, notably specificity to EFRH peptide antigen as noted by Frenkel and suitable reactive antibody thereto. Schenk and Frenkel specifically motivates the artisan to substitute the Aß peptide as the foreign peptide for the purpose of stimulating antibody production for detection and development of compounds to control aggregation of ßAP in vivo, specifically for eliciting antibodies that inhibit aggregation and or cause dissagregation. Fanutti, and Delmastro further evidence the common usage of phage as suitable in vivo vaccine vectors for stimulating an immune response. Frenkel already notes the appropriate epitope construct for antibody production and immunity.

Applicants traverse rejection as set forth at pp. 12-15. Applicants state that Frenkel does not teach the use of bacteriophage for displaying the requisite epitopes of EFRH. In contrast, Frenkel does teach this, see in particular Abstract and Table 1 as noted in the rejection. Applicant's were apparently misled by the Examiner's obvious error (the claim was originally rejected see claim 4) including bacteriophage fd in the negative statement. This has been corrected. In particular, p. 86 nots the phage fd-derived vector. Applicants further argue that there is no suggestion that the vectors be used as a therapeutic vaccine and that the phage are not used as an immunogen. Applicants concede that Bhardwaj would make it obvious to use g VIIIp in the library tool used by Frenkel but that no combination of references arrives at administration of the phage as vaccine. Applicants do acknowledge the teaching of Winters with respect to display of human peptides and antibody fragments on bacteriophage.

Applicant's arguments have been fully considered and the rejection is made non-final and supplemented with the teachings of Schenk noted above in addition to Fanutti and Delmastro evidencing the advanced state of the art in the use of phage display for vaccination purposes in vivo. In particular Fanutti teaches gVIIIp expressing phage fd and Delmastro teach phage13 vaccines to stimulate an immune response in vivo specifically using the intranasal route. Accordingly, the reference teachings render obvious the claimed invention.

Conclusion

17. No claims are allowed.

18. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
September 5, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER

9-5-06